THE CHEMISTRY OF CERTAIN PHENYLHYDRAZONES. ATTEMPTED RING CLOSURE TO CINNOLINES

by

ROBERT KEITH MEYER

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INTRODUCTION

Cinnoline (I) is a nitrogen analog of naphthalene with nitrogen atoms replacing the carbon-hydrogen groups at the number 1 and 2 positions (Structure I). Much less is known of this compound and its derivatives than of the related isomeric phthalazines (II), quinoxalines (III) and quinazolines (IV).

(I)

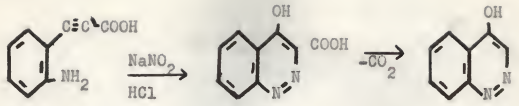
(II)

(III)

(IV)

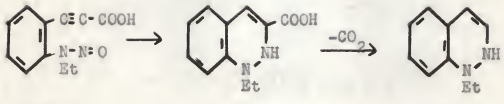
von Richter's synthesis in 1883 (8) of 4-hydroxycinnoline has been accepted generally as the earliest work in this field but the synthesis of "ethyl quinazole" (a dihydrocinnoline) by Fischer and Kuzel (3) takes precedence over von Richter's work by 25 pages in the 1883 edition of the Berichte.

von Richter (8) diazotized 2-aminophenylpropiolic acid (V) and obtained 4-hydroxycinnoline-3 carboxylic acid (VI). This compound decarboxylated when it was heated to its melting point and gave 4-hydroxycinnoline (VIII). Distillation of the 4-hydroxycinnoline with zinc dust gave an impure oil which probably contained some of the parent heterocycle but no pure product could be obtained.



(V) (VI) (VII)

Fischer and Kuzel (3) probably obtained a dihydrocinnoline, which they called "ethyl quinazole" (IX), when N-ethyl-N-nitroso-o-aminocinnamic acid (VIII) was reduced with zinc and acetic acid followed by decarboxylation of the intermediate product. This product (IX) was probably 1-ethyl-1,2-dihydrocinnoline.

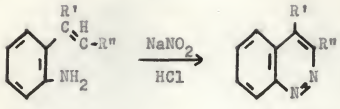


(VIII) (IX)

Shortly after von Richter's original work, Widman (15), diazotized 3-amino-4-isopropenylbenzoic acid (X), ring closure occurred and 4-methylcinnoline-7 carboxylic acid (XI) was the product

(X) (XI)

Some years later Stoermer and Fincke (13) and Stoermer and Gaus (14) showed that this reaction was of general nature and prepared several new cinnolines (XIII) from compounds of the general formula represented by structure XII.



(XII) (XIII)

where:	R'	R"
1.	C_6H_5	H
2.	p-$CH_3C_6H_4$	H
3.	C_6H_5	CH_3
4.	p-$CH_3OC_6H_4$	H

They proved the structures of several of the products by oxidative degradation methods. Stoermer and Fincke (13) and Stoermer and Gaus (14) recognized that the nature of the groups R' and R" controlled the course of the reaction. They stated that when R" contained a carbonyl group the formation of a cinnoline was hindered. This was based on the observation that o-aminocinnamic acid gave no cinnoline upon diazotization. Several other methods were reported which led to highly substituted cinnolines but these were not general in application.

In 1942, Simpson and Stephenson (11) and Simpson and Schofield (9, 10) published the first of a series of papers on the chemistry

of these compounds. This work comprised a careful re-examination and an intensive study of several of the more general cinnoline preparations. In this work, Simpson and Stephenson (11) and Simpson and Schofield (9, 10) have prepared more cinnolines than all previous investigators and thus have accumulated a great deal of chemical and physical data with respect to these compounds and their preparations. They re-examined the Widman-Stoermer reaction and showed it to be a general reaction within certain limits as to structural features of the starting compound (XII). They found that cinnolines were obtained when R' was aryl regardless of the character of R". When R" was aryl or some other negative group, such as the cyano- or carboxyl group, and R' was hydrogen or carboxyl, no cinnoline was obtained. With compounds where R" was aryl, diazotization generally led to the formation of phenanthrene derivatives.

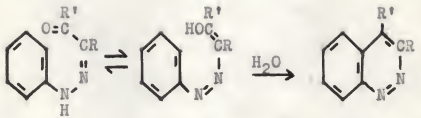
In 1946, Leonard et al. (6) reported the synthesis of a number of cinnolines which were designed to replace the quinoline ring in antimalarial test compounds. The procedures employed were similar to the Widman-Stoermer (13,14,15) method.

Simpson usually diazotized the amines and heated the resulting diazonium salt solution to effect ring closure. Leonard et al. diazotized the amines in water or acetic acid solution and allowed them to stand in the dark until the solution no longer gave a positive test with -naphthol. This required from 2 to 60 days.

A consideration of this general reaction as employed by Simpson and Leonard to prepare cinnolines shows that it is restricted to the preparation of only a few types of cinnolines. If a second

general method could be devised, many more substituted cinnolines could be prepared and studies of the chemistry of this heterocyclic system would be broadened.

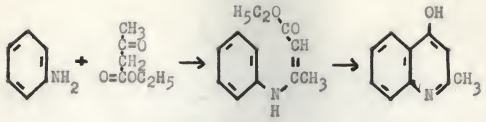
An attractive possibility for cinnoline synthesis is suggested by the structure of the phenylhydrazones prepared by the coupling reaction of diazonium compounds with active-methylene type compounds. The general structure of these products is represented by XIV. In order to obtain a cinnoline (XVI), a loss of water by XV (the tautomer of XIV) with formation of a carbon-carbon bond is all that seems



(XIV) (XV) (XVI)

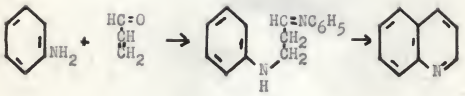
necessary. Other generalized formulas similar to XIV can be written for these starting compounds and cinnoline preparation seems feasible by simple loss of water, alcohol or carbon dioxide. These coupled products (XIV) as possible starting materials for cinnoline synthesis have been examined by Leonard, Boyd and Herbrandson (6).

These workers summarized the postulated course of synthesis by analogy to a number of quinoline syntheses. The Conrad-Limpach reaction (2) involves the condensation of acetoacetic ester and aniline followed by thermally induced ring closure, as shown by structures XVII and XVIII.



(XVII) (XVIII)

The Skraup reaction involves the condensation and oxidative ring closure of aniline and acrolein, as shown by formulas XIX and XX.



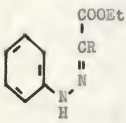
(XIX) (XX)

A modification of this reaction is represented by structures XXI and XXII.

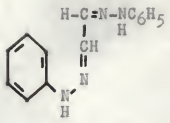
(XXI) (XXII)

Leonard, Boyd and Herbrandson (6) employed the conditions used in these quinoline syntheses for the analogous hydrazone structures and in each case obtained negative results. They attempted to cyclize the following substances (XXIII), (XXIV) and

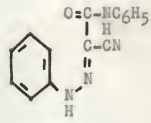
(XXV) which were, respectively, analogous to the starting compounds discussed previously.



(XXIII)



(XXIV)



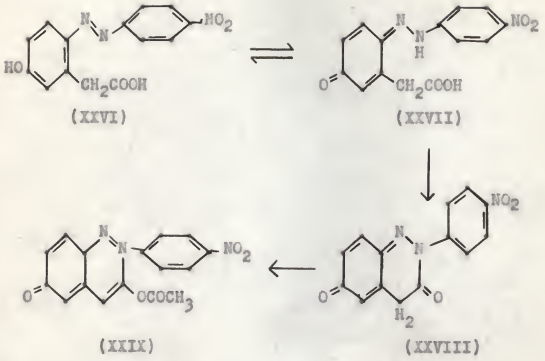
(XXV)

In regard to attempted cyclizations of hydrazones of the type represented by formula XXIII, Leonard et al. (6) worked with the following derivative. Ethyl cyanoglyoxylate m-chlorophenylhydrazone (XXIII, R was CN, a Cl atom meta to -NH- group) and diethyl mesoxalate m-chlorophenylhydrazone (XXIII, R was COOEt, Cl meta to -NH- group) were prepared by coupling diazotized m-chloroaniline with cyanoacetic ester, acetoacetic ester and malonic ester, respectively. No cinnoline formation was observed when these substituted phenylhydrazones were heated in an inert solvent under wide ranges of temperature and heating time. When decomposition did not occur, only starting material was recovered.

The experiments conducted by Leonard et al. (6) with hydrazones similar in structure to formulas XXIV and XXV will not be discussed here since the work reported in this thesis has to do with structures similar to XXIII only.

More recently, Kornfeld (5) reported the apparent synthesis of a cinnoline in his experiments to produce heterocyclic-steroid analogs. No proof other than a carbon-hydrogen analysis was given.

In his work, m-hydroxyphenylacetic acid (XXVI) was coupled in alkaline solution with diazotized p-nitroaniline to form the azo dye (XXVI) in normal fashion.



(XXVI) (XXVII)

(XXIX) (XXVIII)

The azo compound was subjected to the action of acetic anhydride in the presence of sulfuric acid, as catalyst, and from the resulting reaction mixture a non-acidic, yellow crystalline product was isolated in good yield. The analyses showed one acetyl group had been elimated under the acetylating conditions.

According to Kornfeld (5), further investigations showed the reaction was quite general and a number of diazotized aromatic amines were cyclized easily to cinnoline derivatives similar to (XXIX). He postulated that the steps involved first a cyclization of the azo compound (XXVI) in its tautomeric form (XXVII) to 2-p-

nitrophenyl-3,6-diketo-2,3,4,6-tetrahydrocinnoline (XXVIII) and then acetylation of the enol form of (XXVIII) to yield 2-p-nitrophenyl-3-acetoxy-6-keto-2,6-dihydrocinnoline (XXIX).

It was felt that Leonard et al. (6) had not exhausted the possibilities of conditions which might lead to ring closure of the compounds of the type represented by formula (XXIII). Accordingly, compounds of this general type were synthesized and attempts were made to effect ring closure and the results are reported in this thesis.

EXPERIMENTAL

Preparation of Materials

Ethyl 2,3-Dioxobutanoate 2-Phenylhydrazone. This compound was prepared in large quantity by a modification of the method of Kjellin (4). Aniline (47 gm, 0.5 mole), hydrochloric acid (125 ml, conc.) and water (125 ml) were mixed, ice was added and sodium nitrite (36 gm, 0.5 mole) was rapidly stirred into the solution. This solution was stirred rapidly into an ice-cold solution of ethyl alcohol (300 ml, 95 per cent), ethyl acetoacetate (65 gm, 0.5 mole), sodium acetate (125 gm, excess) and approximately 1500 ml of ice and water. The product separated immediately and was removed by filtration. It was recrystallized from ethyl alcohol-water mixture. The product was a yellow crystalline solid (86 gm, 74 per cent of theory) with a m. p. 86-87° C. A m. p. of 80-84° C was reported by Kjellin (4) for this compound.

In this way, a total of 486 gm of this substituted hydrazone was prepared in a number of subsequent runs.

Ethyl 2,3-Dioxobutanoate 2-(N-Acetyl)-phenylhydrazone. A 25 gm portion of ethyl 2,3-dioxobutanoate 2-phenylhydrazone and acetic anhydride (100 ml) which had been chilled and contained 1.0 ml of sulfuric acid were mixed together and the mixture was allowed to stand overnight. Ice was added to hydrolyze the excess acetic anhydride and the mixture was allowed to warm up to room temperature. The N-acetyl derivative was removed by filtration and was washed with water until no odor of acetic acid was noticeable on the precipitate. Recrystallization of the product from acetone gave 19.6 gm (78 per cent) of a white crystalline solid with a m. p. of 118-119° C. Hailer and Bulow (1) reported a m. p. of 119-120° C. for this compound.

In a similar manner, a total of 50 gm of the acetyl derivative was prepared in subsequent runs.

Ethyl 3-Phenyl-2,3-dioxopropanoate 2-Phenylhydrazone. This compound was prepared by a modification of the method of Stierlin (12). Aniline (47 gm, 0.5 mole), hydrochloric acid (125 ml, conc.) and water (125 ml) were mixed, ice was added and sodium nitrite (36 gm, 0.5 mole) was rapidly added to the solution. This solution was stirred rapidly into an ice-cold solution of ethyl benzoylacetate (96 gm, 0.5 mole) in ethyl alcohol (300 ml, 95 per cent) and approximately 1500 ml of ice and water. The product separated as a red oil which slowly solidified to an orange solid. This was recrystallized from ethyl alcohol to give 97 gm (65 per cent) of pro-

duct with a m. p. of 66-68° C. Stierlin (12) reported a m. p. of 65° C for this compound.

Ethyl 2,3-Dioxobutanoate 2-(p-Nitrophenylhydrazone). This compound was prepared in a manner similar to the previously described coupling reactions. A portion of p-nitroaniline (75 gm, 0.5 mole), hydrochloric acid (125 ml, conc.) and water (125 ml) were mixed, ice was added and sodium nitrite (36 gm, 0.5 mole) was stirred in rapidly. This solution was stirred into an ice-cold solution of ethyl acetoacetate (65 gm, 0.5 mole) in ethyl alcohol (300 ml, 95 per cent), sodium acetate (125 gm) and approximately 1500 ml of water and ice. A yellow precipitate formed immediately and was filtered off after the solution was allowed to warm up to room temperature. Recrystallization from ethyl alcohol gave a yellow solid (110 gm, 80 per cent) with a m. p. of 125-126° C. Kjellin (4) reported a m. p. of 122-123° C. for this compound.

Attempted Cyclizations under Various Conditions

Heat. Ethyl 2,3-dioxobutanoate 2-(N-acetyl)-phenylhydrazone (5.0 gm) was placed in a Carius tube and heated at 150° C. for two hours. The Carius tube was broken open and the solid was extracted with ether. A white solid was recovered with a m. p. of 118-119° C. This gave no depression in m. p. when mixed with the original N-acetyl compound.

A 5.0 gm sample of the same N-acetyl derivative was heated for two hours at 210° C. A solid with m. p. of 108° C was removed from

the tube and upon recrystallization from acetone gave a m. p. of 117-118° C. This was identical with the starting material.

A 5.0 gm sample of the N-acetyl derivative was heated for two hours at 250° C. The tube was opened and the tarry decomposition products were removed but no pure product could be isolated.

A 5.0 gm sample of the same derivative was heated for four hours at 160-175° C. The solid was removed from the tube and had a m. p. of 118-120° C and was identical with starting material.

Sulfuric Acid. Ethyl 2,3-dioxobutanoate 2-(N-acetyl)-phenylhydrazone (1.0 gm) was dissolved in sulfuric acid (75 per cent) and heated under reflux for an hour. The solution turned black and no pure product could be isolated from the reaction mixture.

A sample of the same acetyl derivative (1.0 gm) dissolved in sulfuric acid was heated on a water bath at 50° C for forty-five minutes. The solution turned black again and no pure product could be isolated.

Ethyl 3-phenyl-2,3-dioxopropanoate 2-phenylhydrazone (1.0 gm) was dissolved in 50 ml of sulfuric acid (78 per cent) and was kept at 50° C for one hour. The solid obtained had a m. p. of 61-62° C and was identical with starting material.

Ethyl 3-phenyl-2,3-dioxopropanoate 2-(N-acetyl)-phenylhydrazone (2.0 gm) was dissolved in 50 ml of sulfuric acid (conc.) and was kept at 50-52° C for two and one-half hours. The product isolated from the solution was insoluble in water, sodium hydroxide solution, hydrochloric acid and concentrated sulfuric acid. It had a m. p. of 92-95° C. Further attempts to characterize this compound were unsuccessful.

Acetic Anhydride. Ethyl 2,3-dioxobutanoate 2-(N-acetyl)-phenylhydrazone (2.0 gm) was dissolved in acetic anhydride (25 ml) and was refluxed for two hours. There was no apparent reaction of any kind and the starting material was recovered unchanged.

Ethyl 2,3-dioxobutanate 2-(N-acetyl)-phenylhydrazone (2.0 gm) was dissolved in glacial acetic acid (5 ml) and acetic anhydride (5 ml) and was refluxed for one hour. The product precipitated upon dilution with water and had a m. p. of 98-112° C. However, further purification of this solid was unsuccessful.

Acetic Anhydride and Pyridine. Ethyl 2,3-dioxobutanoate 2-(p-nitrophenylhydrazone) (20 gm), acetic anhydride (30 ml) and dry pyridine (40 ml) were mixed in a 250 ml standard taper round bottom flask equipped with a reflux condenser. The mixture was refluxed five hours and was allowed to cool to room temperature. It was poured into a mixture of hydrochloric acid and ice in order to hydrolyze the excess acetic anhydride. A brownish-black precipitate separated and was subjected to repeated recrystallizations from acetone. A brown colored precipitate with a m. p. of 196-198° C was obtained. Following recrystallization from acetone (with charcoal treatment) the white product (approx. 2.0 gm, 10 per cent) was obtained with a m. p. of 198-199° C. Varying conditions were employed in these experiments. The same product was obtained from mixtures which had refluxed for five or seven hours but none was obtained when the reflux period was shorter than three hours. When the amount of pyridine was cut to 5 ml, the odor of ethyl acetate was very strong when the mixture was poured on to ice. Evidently,

decomposition of the hydrazone had resulted because no pure product could be isolated.

Equimolar ratios of pyridine and acetic anhydride were used but the yield of the high melting product was not improved. However, the amount of decomposition products appeared to be less and were easier to remove during recrystallization. In this way, a total of 8.4 gm of the light brown solid was prepared and after recrystallization from acetone (with charcoal treatment) there was obtained 4.72 gm of a white solid with a m. p. of 198-199° C.

In all preparations the major quantity of the starting material was converted to a brownish-black tar from which the white product was tediously isolated by extensive recrystallizations.

Preliminary Study of Product Obtained from the Acetic Anhydride and Pyridine Mixtures

Carbon-Hydrogen-Nitrogen Analyses. The carbon and hydrogen content of the white compound (m. p. 198-199° C) was obtained by microanalytical combustion analysis. The nitrogen was obtained by a micro-Dumas method (7). The following values were obtained: carbon, 55.44 and 54.80 per cent; hydrogen, 4.48 and 3.79 per cent; and nitrogen, 13.78 per cent.

Molecular Weight. A molecular weight by the melting point depression of camphor (Rast method) was determined. A 0.0414 gm sample of the white solid with a m. p. of 198-199° C was mixed with camphor (0.5406 gm). The camphor had a m. p. of 178.4° C (an average of three separate m. p. determinations). The m. p. of the fused

sample (average of eight determinations) was 168.0° C. The depression (T) was therefore 10.4° C. The molecular weight was calculated by the following equation.

$$\frac{40 \text{ (wt. of compd.)} \quad 1000}{T \text{ wt. camphor}} = M$$

The molecular weight was found to be 294.

Saponification Equivalent. In a typical experiment, a sample of the compound (0.0805 gm) was refluxed with 13.0 ml of 0.1521 N sodium hydroxide. The excess NaOH was back-titrated with 15.60 ml of 0.1004 N sulfuric acid, as estimated from the curve obtained by the plot of pH versus ml of acid. The titration was followed with a Fisher Titrimeter. The saponification equivalent was calculated as follows:

(15.6)(0.1004) = 1.56624 m.e. acid added

(13.0)(0.1521) = 1.9773 m.e. base added

(1.9773-1.56624)= 0.4111 m.e. used up in saponification

S. E.= (0.0805)(1000)/0.4111 = 196

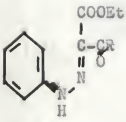
Other weighed samples were employed and the saponification equivalents were 205, 300 and 206.

DISCUSSION AND CONCLUSIONS

The preparations of the starting compounds for the projected ring closure were simple and, in general, resulted in excellent

yields of the highly substituted hydrazones. Several of the lower melting compounds were difficult to purify but all were obtained eventually as crystalline solids.

Leonard et al. (6) have published the only report found in the literature which dealt with the possible use of these hydrazones as starting materials for cinnoline syntheses. In all cases examined they reported negative results insofar as cinnoline formation was concerned. The problem which is reported herein was a re-examination and extension of their studies of the type of compound represented by formula XXIIIa.

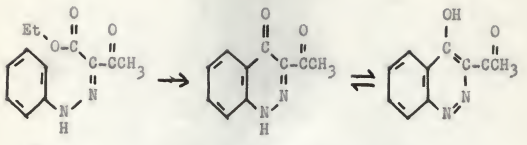


(XXIIIa)

They attempted to cyclize this type of compound by thermal means only, by analogy to the Conrad-Limpach (2) syntheses of quinolines from a compound of related structure, as described previously. It was thought that a more extensive examination of this synthesis by analogy would be fruitful.

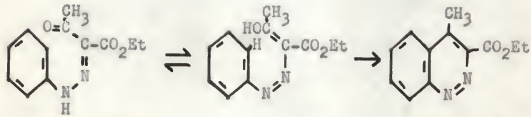
In the work in this laboratory, it was considered that if ring closure occurred with the formation of a cinnoline it could occur in two possible ways. Ethyl 2,3-dioxobutanoate 2-phenylhydrazone (XXX) was examined first. The ring closure could occur with loss

of alcohol as follows,



(XXX) (XXXI)

or by loss of water from an enol-form of XXX, as shown by the following equations:



(XXXII) (XXXIII)

Thermal treatment of samples of XXX in sealed tubes at 150° C and 210° C failed to alter the starting compound, and at 250° C extensive decomposition occurred. This, of course, confirmed the results reported by Leonard et al. (6).

It was thought then that a powerful condensing agent or dehydrating agent such as sulfuric acid might have the proper effect on such compounds in that it would tend to associate with water or alcohol molecules as they were formed and thus prevent reversal of the reactions represented by the preceding equations. This was an

extension beyond the work of Leonard et al. (6). Application of these conditions to compound (XXX) resulted in no reaction or in complete decomposition.

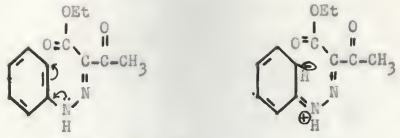
Examination of the structure of compounds of the type represented by XXX (or XXIIIa) suggested that several mesomeric electronic shifts could occur. The parent molecule XXX has a pair of unshared electrons on the amino-type nitrogen (-NH-) rendering that group relatively basic in nature. These electrons could shift mesomerically into the side chain portion of the molecule, perhaps sufficiently to stabilize the molecule so that the energy requirement for the cyclization would be too high. This shift would be represented by the following formulas (XXXIV):

(XXXIV)

In addition, a second electron sink would be available for this mesomeric shift of electrons into the side chain, which shift is represented by the following pair of structures (XXXV).

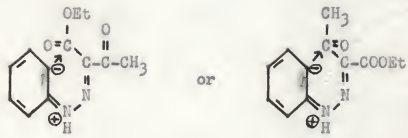
(XXXV)

Both of these shifts would be in opposition to a shift into the benzene ring as represented by the formulas (XXXVI)



(XXXVI)

The latter shift would be the one which might be expected to aid ring closure since the negative charge at the ortho position might tend to attract the relatively positive carbon of the carbonyl group in the carbethoxyl group or in the acetyl group. This possibility is represented by structures (XXXVI) and (XXXVII), respectively.

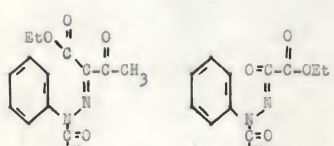


(XXXVI) (XXXVII)

As mentioned previously, the electronic shifts into the side chain would be in opposition to the shift into the aromatic nucleus and possibly would inhibit ring closure for two reasons. If the tendency for development of the negative charge at the ortho position is

lowered by such shifts into the side chain, the attraction of an ortho carbon for the relatively positive carbon of a carbonyl group would be lessened. In addition, this shift into the side chain possibly would tend to diminish the positivity of the carbon atom of a carbonyl group by positive charge transfer down the chain to the amino-type nitrogen and the tendency for reaction with the ortho carbon would be diminished still further. If this was the case, then it was thought that an alteration of the structure of (XXX) which would bind the electron pair of the amino-type (-NH-) group more tightly would cut down on the side chain shifts and perhaps increase the cyclization tendency.

Employing this reasoning the N-acetyl derivative (XXXVIII) of ethyl 2,3-dioxobutanoate 2-phenylhydrazone was prepared and subjected to various conditions which might lead to ring closure.



(XXXVIII)

The acetyl group on the amino-type nitrogen ($-N(COCH_3)-$) would tend to bind the unshared pair of electrons more tightly, a fact which seemed to be verified by the absence of color of this derivative as compared to the yellow or orange color of the parent

compound. Development of color in the latter thus would be attributed to electron shifts in the excited state which would increase the length of the conjugated system and would result in absorption of longer wavelengths of light. The N-acetyl group apparently diminishes this electron shift into the side chain to the extent that excited state structures similar to those of the original do not form, hence the absence of color.

As in the case of the parent compound those conditions which were tried, heat and sulfuric acid, either failed to alter the compound or resulted in complete decomposition. The reasoning which led to these experiments was logical, perhaps, but obviously the alteration of structure employed was not of the kind or degree which would aid ring closure.

The milder dehydrating agent acetic anhydride failed to alter either the parent compound or the N-acetyl derivative when each was refluxed in acetic anhydride.

When a mixture of acetic anhydride and pyridine containing ethyl 2,3-dioxobutanoate 2-(p-nitrophenyl hydrazone) was refluxed this latter compound was converted into at least two molecular species. The mixture was poured into aqueous acid in order to convert the pyridine to its hydrochloride and to hydrolyze the acetic anhydride. The product was a brown to black solid and was removed by filtration. Apparently the major portion of the starting compound was converted to a brown or black substance which defied attempts to obtain in a pure state. A second product was obtained in yields which averaged about 10 per cent based on the quantity of starting material employed. This product was obtained eventually

as a white crystalline solid, but only after a long and tedious sequence of recrystallizations from acetone and water mixtures. A combined yield of 4.72 gm of the colorless product was obtained from about 100 gm of starting material. In view of the small quantity of this product, and the time required to prepare it only preliminary structure studies were possible.

Carbon and hydrogen percentages were obtained by combustion microanalyses for two samples which evidently were of different purity. The values observed were carbon, 55.44 and 54.80 per cent, and hydrogen, 4.48 and 3.79 per cent. A nitrogen analysis was made by the micro-Dumas (7) method and the observed value was 13.78 per cent.

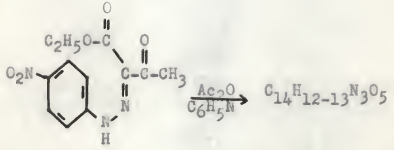
The molecular weight was determined by the Rast melting point depression method in camphor and the observed value was 294.

It seemed initially that the three nitrogens that were originally in each molecule of the starting material remained in this colorless solid. The empirical formula was calculated as follows:

Carbon:	$\frac{55.12}{12.01} = 4.58$	$\frac{4.58}{0.983} = 4.66$
Hydrogen:	$\frac{4.13}{1.008} = 4.10$	$\frac{4.10}{0.983} = 4.17$
Nitrogen:	$\frac{13.78}{14.008} = 0.983$	$\frac{0.98}{0.98} = 1.00$
Oxygen:	$\frac{26.97}{16.00} = 1.68$	$\frac{1.68}{0.983} = 1.71$

From this, the empirical formula is $C_{4.66}H_{4.17}NO_{1.71}$. If the three nitrogen atoms present in the starting material were still present in this product the above relative values would be multiplied by three in order to obtain the molecular formula $C_{13.98}H_{12.51}N_3O_{5.13}$ which in turn would indicate a true formula of $C_{14}H_{12-13}N_3O_5$. The molecular weight calculated for this formula was 302-303 which checked very well with the observed molecular weight of 294 obtained by the Rast method.

If the analytical data are reliable, then the following formulation is valid. From this it is apparent that two carbon atoms,



and perhaps one or two hydrogen atoms, were gained during the reaction. A rather strange fact is that the number of oxygen atoms did not increase, a fact which obscured the course of the reaction. As yet an explanation of these results cannot be given until more data is available.

There was time for only one set of saponification experiments. The white product dissolved slowly in hot alkali, a behavior characteristic of esters, and considerable color was produced. The saponification mixtures were back-titrated with standard acid and the titration was followed by means of a Fisher Titrimeter. The endpoint

was estimated in the usual manner employed for potentiometric titrations. The results were disappointingly inconclusive with one value about 300 and three additional values around 200.

Certainly, more information must be obtained for this compound before a structure may be postulated. However, this product does provide a basis for additional work in the future.

SUMMARY

Heat, sulfuric acid and acetic anhydride failed to effect cyclization to cinnolines of some hydrazones obtained by the coupling of aromatic diazonium salts with active methylene compounds, nor was cyclization effected of certain derivatives of these hydrazones. Hot acetic anhydride and pyridine mixtures converted ethyl 2,3-dioxobutanoate 2-(p-nitrophenylhydrazones) to a dark colored material, which defied attempts at purification, and to a small yield of a colorless product which has been subjected to preliminary studies of structure. This product may be a cinnoline but insufficient data are available at present for accurate designation of its structure.

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